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# THE INJECTIONS OF HETEROLOGOUS STREPTOCOCCI, KILLED BY GALACTOSE, IN ERYSIPELAS AND IN SCARLET FEVER.\*

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IN view of apparently favorable results obtained by Weaver and Tunncliffe (p. 589), in cases of subacute and chronic infections by streptococci in which injections of homologous streptococci, killed by suspension in 25 per cent solution of galactose, were employed, it seemed desirable to try the effects of similar injections in a larger series of cases. Cases of erysipelas and scarlatina were selected for this study. Since it was necessary to make the injections as soon as possible after the cases came under observation, mixtures of streptococci from similar cases previously isolated and killed were used. The streptococci were treated in the manner described in the article mentioned. Special acknowledgment is made of the courtesy of Dr. Baum and Dr. Cameron, who kindly allowed the use in the Cook County Hospital of their cases for this study.

## THE EFFECTS OF THE INJECTION OF POLYVALENT HETEROLOGOUS STREPTOCOCCI KILLED BY SUSPENSION IN 25 PER CENT GALACTOSE SOLUTION IN CASES OF ERYSIPELAS.

The streptococci employed in the cases of erysipelas were obtained as follows: Pure cultures of typical hemolyzing streptococci were obtained from the nasal secretions of three cases of typical uncomplicated erysipelas and from the purulent discharge from a wound of the face complicated by typical spreading erysipelas. Equal quantities of streptococci from the four strains grown upon blood agar were suspended in 25 per cent galactose solution until the suspensions were sterile, when the suspension was distributed in small test-tubes, the clear fluid pipetted off after thorough centrifugalization, and the sediment rapidly dessicated in vacuum. The tubes were then sealed and kept in the ice-box until used. For injection the bacteria were

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suspended in 0.85 per cent salt solution. The dose injected contained about 200,000,000 killed streptococci.

Twenty-two cases of erysipelas received injections. Of these two were relapsing, six migrating, and three recurrent; of the rest, three were mild, four moderate, and six severe. Four involved the leg, and 18 the face. In all but three cases a single injection was given. In one case two injections were given, in one three injections, and in one recurrent case injections were given in several attacks.

Owing to the irregular course of the disease and the numerous clinical types met with, all of which may closely resemble each other in the initial stages, it is very difficult to judge of the effects of treatment. In only three cases of the series did the treatment appear to have any desired effect. All three were of the "migrating" type, one of the leg and two of the face. In all the spreading stopped within two days, and the patients made a rapid recovery. No opinion could be formed as to any action the treatment might have in preventing complications, as only four cases of abscess were met with, two in injected and two in uninjected cases. No other complications occurred. In the three cases that were known to be recurrent, the treatment did not prevent later recurrences. One case, which received several injections, had five attacks of typical facial erysipelas during eight months, the first attack lasting six weeks. Bacteriological examination during the first attack showed the nasal secretions to contain very few streptococci, and during the last two attacks streptococci could not be cultivated from the nasal secretion nor from the contents of vesicles developing during the course of the disease.

At the site of injection slight tenderness for 24 hours was sometimes observed, but no other local or systemic effect was noted. Systematic determinations of the opsonic index were not made. In one case the index rose from 1.0 on the day of the injection, to 4.0 on the third day following. In another case there was a rise from 1.0 to 2.1. In two cases the index seemed unaffected.

From our experience in these cases we are forced to conclude that the injection of killed polyvalent heterologous streptococci during the acute stage of erysipelas is without apparent effect upon the course of the disease, the cases doing no better than the controls which received no injections. That this would have been the case might

have been predicted since it was shown by Weaver and Tunicliff that in rabbits several days are required for immunity to appear following the injection. By the time such immunity has developed the patient's body may already have developed the immune bodies and gone through the reactions that led to recovery in the natural course of the disease.

In the three cases of the "migrating" type in which the course was more prolonged, the injections appeared to have a beneficial influence. The recurrent cases were under observation only until recovery from the acute attacks was complete. It is not unlikely that several injections with increasing doses would finally stimulate a sufficient degree of immunity to prevent further recurrence in such patients. In these cases it would be desirable to use streptococci isolated from the patient.

THE EFFECTS OF THE INJECTION OF POLYVALENT, HETEROLOGOUS  
STREPTOCOCCI KILLED BY SUSPENSION IN 25 PER CENT  
GALACTOSE SOLUTION IN CASES OF SCARLATINA.

The streptococci employed in the cases of scarlatina were isolated from the tonsils in acute cases, from purulent secretions from scarlatinal otitis media, from the pus in suppurative mastoiditis, and from the pus of suppurating cervical glands developing during the course of scarlatina. The growths from various cultures were mixed and prepared as in the case of erysipelas.

The investigation was conducted in connection with the cases admitted in the hospital during the months of April to September, 1908. In all 274 cases were under observation, of which 116 received the injections and the remaining 158 were considered as controls. The cases which received the treatment were selected at random, and not more than half the cases admitted during any one month were injected. While it was not expected that such injections would materially alter the course of the disease it was hoped that they would favorably influence the occurrence or duration of complications due to pyogenic organisms.

*Cases injected during the acute stage.*—Eighty-eight cases were injected during the acute stage of the disease before the occurrence of any purulent complications, and were studied with reference to the possible effect of the injections in preventing such complications.

Complications here considered are purulent rhinitis, otitis media, mastoiditis, severe cervical adenitis (suppurative and non-suppurative), and arthritis.

*Results.*—The following summary shows the number of cases with the most common complications and the percentages which they constitute of the entire number of each group:

TABLE 1.

	INJECTED		NOT INJECTED	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Rhinitis.....	7	8	28	18
Otitis media.....	12	13.6	16	10
Cervical adenitis.....	5	6	16	10
Cervical abscess.....	1	1	5	3
Total cases*.....	20	23	48	31

\* The total number of cases does not correspond to the sum of those showing various complications since some cases had more than one complication.

This table seems to indicate, in the injected cases, a reduction in the percentage of all of the complications except otitis media, which, however, is by far the most frequent and important. But the series, as they stand, are not strictly comparable as shown in the following summary of the total number of cases, classified according to their severity, and the percentage of each series thus falling in each class.

TABLE 2.

	MILD		MODERATE		SEVERE		TOTAL CASES
	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	
Injected.....	37	42	44	50	7	8	88
Not injected.....	73	48	65	41	20	13	158

Thus the control cases are shown to have an unduly large proportion of severe cases, which would, in part at least, account for the higher percentage of complications, since the largest number of complications is found in the severe cases as shown by the next summary in which the complicated cases are classified according to the severity of the original disease, the figures giving the percentage of cases in each class.

TABLE 3.

	MILD		MODERATE		SEVERE		TOTAL CASES
	No. of Cases	Per Cent	No. of Cases	Per Cent	No. of Cases	Per Cent	
Injected.....	3	8	13	30	4	57	20
Not injected.....	15	20	20	31	13	65	48

But there are two other factors which tend to distort results. A certain number of cases which were not injected when they came in developed complications later, and were then injected, and considered as "late injected" cases. Thus the non-injected cases, as they stand, do not represent the normal, but are a selected group of cases from which a few (16) complicated cases have been taken. Furthermore, a certain number of cases were already complicated when first seen and hence could not be included among the "injected early" group, but it would not be fair to include these among the controls, since they are a group in which it would be quite impossible to test the prophylactic properties of the injections. Revising these figures, then, so as to omit all cases showing complications during the first week of the disease, and adding to the control cases those that were not injected until late in the disease, we have the following:

TABLE 4.

	No. of Cases	Per Cent
Mild.....	74	48
Moderate.....	67	42
Severe.....	16	10
Totals.....	157	100

The revised figures to show the total number of complications and percentages of cases in each class which became complicated are given in Table 5.

TABLE 5.

	No. of Comp.	Per Cent
Mild.....	16	22
Moderate.....	18	27
Severe.....	9	56
Totals.....	43	27

Thus comparing Table 4 with Table 2 it is seen that the disproportion in the number of severe cases is so reduced as to make the

two series fairly comparable; and comparing Table 5 with Table 1 it is seen that the difference in the percentages of total complications in the two series is so small as to be negligible. The only effect of the injections seemed to be that in those injected cases in which complications arose they occurred on an average of eight days later than in the control cases.

From these results we may conclude that the injection of killed streptococci during the acute stage of scarlatina does not lead to the production of any considerable amount of antistreptococcus immunity. It may be that during this stage the capacity of the body to produce antibodies has been reduced by the scarlet fever infection.

*Cases injected after complications were present.*—Injections in cases in which complications were already present yielded much better results. Thirty-one cases were so treated, a few of them being injected more than once, and 11 (36 per cent) showed prompt improvement. The effect was much more marked in the subacute and chronic conditions than in the acute ones. Of nine cases injected during the first week of the fever, only one showed any immediate improvement. Of 23 cases injected later, 10 (44 per cent) showed prompt improvement. Of 18 cases injected during the first week of the complication eight (33 per cent) showed prompt improvement. Of 16 cases injected later seven (44 per cent) showed prompt improvement. The improvement was shown in a sharp reduction in the amount of discharge (from ears, nose, or cervical abscess), in from two to six days after the injection. In some instances the discharge would cease completely in this time, and in others a very slight discharge would continue for a week or two, then cease. In two instances a nasal discharge which had resisted local treatment for two weeks, had ceased completely five days after injection. In one case an aural discharge which had lasted for more than a month without any indication of improvement stopped completely two days after the injection. Such instances of rapid improvement while occasionally met with in the uninjected cases were usually followed later by a more profuse discharge. One case had purulent discharge from ears, nose, and eyes, a pustular dermatitis as a result of the discharges, superficial ulcerations on lips and tongue, and a general septic condition. These had resisted local and general treatment, and the boy

was getting worse. Three days after an injection he showed a very marked local and general improvement. The evidences of sepsis had disappeared, the nasal and ocular discharges had ceased, the aural discharge was much less, and the skin lesions were healing rapidly, and six days after the injection the aural discharge had ceased completely. The ulcerations on the tongue, however, lasted two or three weeks.

In two or three cases a cervical gland suppurated soon after the injection but even if this result could be ascribed to the injection, the danger is remote because of the large number of similar cases in which no such result occurred. Aside from this, no bad result of any kind was observed as a result of the injections. In the treatment of the later streptococcus complications in scarlatina, it is not unlikely that better results would follow the use of homologous streptococci in preparing the material for injection, and it would be desirable to repeat the injections at intervals of five to seven days, the dose being increased from 200,000,000, to 500,000,000 or 800,000,000. In rabbits the larger doses seemed to produce more reaction and greater immunity, and it is probable that this would hold true in man. Too large initial doses are, however, to be avoided because of the temporary reduction in resistance which may follow and may explain the slight aggravation of discharges and other symptoms sometimes occurring on the day after injections, and the apparent hastening of suppuration in swollen glands in occasional instances.

#### CONCLUSIONS.

1. The injection of polyvalent, heterologous streptococci killed by chemically indifferent agents during the acute stage of erysipelas has no appreciable effect upon the course of the disease. In cases running a prolonged course such injections appear to exert a favorable effect.
2. The injection of such streptococci during the early stages of scarlet fever does not prevent the later development of local streptococcus complications, although they may appear a little later in the disease.
3. The injection of such killed streptococci after local streptococcus complications have developed in scarlatina exerts considerable in-



fluence in hastening recovery. The later the complications appear, the better the results following the injections.

4. Homologous streptococci are probably preferable for preparing the material for injection both in protracted, subacute, chronic, and recurring cases of erysipelas and in cases of scarlatina with local streptococcus infection.